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Laursen, Janne Marie; Schoof, Erwin; Søndergaard, Jonas Nørskov; Linding, Rune; Pedersen, Susanne Brix

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Identification of a novel immunoregulatory signaling pathway exploited by M. tuberculosis in dendritic cells

Author Block: Janne Marie Laursen, E. Schoof, J.N. Søndergaard, R. Linding, S. Brix;
Kgs. Lyngby, Denmark

Abstract:
The causative agent of tuberculosis, M. tuberculosis, has infected over a third of the world's population and the persistence of latent infections poses a massive burden to health care systems and human well-being. The dendritic cell (DC) plays a crucial role in shaping the nature of the adaptive immune response after exposure to pathogens, and the interaction between M. tuberculosis and the dendritic cell is of profound importance for the course of infection. During their interaction, the DC is exposed to multiple M. tuberculosis-derived ligands recognized by a range of pattern recognition receptors, but the result is typically an immune response that is not very effective at clearing the bacteria from the host. The reason why the induced immune response is ineffective at clearing the bacteria is not fully understood, but clues may be given in the signaling pathways induced in DCs upon M. tuberculosis-exposure.
High resolution LC-MS/MS was used for a global analysis of the proteome and the phospho-proteome in human DCs upon stimulation with intact M. tuberculosis or purified lipopolysaccharide (LPS). Data were analyzed using MaxQuant and Python, and the algorithm NetworKIN was used for prediction of kinases responsible for the observed phosphorylation sites.
Multiple phosphorylation sites and protein kinases were identified that validate previously identified intracellular signaling structures induced in DCs by M. tuberculosis. Importantly, from the MS data analysis, FMS-related tyrosine kinase 3 (FLT3), that signals through JAK2 and STAT3, was identified as a novel protein kinase potentially activated in DCs by M. tuberculosis.
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ICI 2013 Abstract Submission c/o Vienna Medical Academy
Alserstrasse 4, 1090 Vienna Austria
Phone: +43 1 405 13 83 13
Fax: +43 1 407 82 74

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